Oral sodium phenylbutyrate in patients with recurrent malignant gliomas: A dose escalation and pharmacologic study[1]

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We determined the maximum tolerated dose (MTD), toxicity profile, pharmacokinetic parameters, and preliminary efficacy data of oral sodium phenylbutyrate (PB) in patients with recurrent malignant gliomas. Twenty-three patients with supratentorial recurrent malignant gliomas were enrolled on this dose escalation trial. Four dose levels of PB were studied: 9, 18, 27, and 36 g/day. Data were collected to assess toxicity, response, survival, and pharmacokinetics. All PB doses of 9, 18, and 27 g/day were well tolerated. At 36 g/day, two of four patients developed dose-limiting grade 3 fatigue and somnolence. At the MTD of 27 g/day, one of seven patients developed reversible grade 3 somnolence. Median survival from time of study entry was 5.4 months. One patient had a complete response for five years, and no partial responses were noted, which yielded an overall response rate of 5%. Plasma concentrations of 706, 818, 1225, and 1605 μM were achieved with doses of 9, 18, 27, and 36 g/day, respectively. The mean value for PB clearance in this patient population was 22 liters/h, which is significantly higher than the 16 liters/h reported in patients with other malignancies who were not receiving P450 enzyme–inducing anticonvulsant drugs ($P = 0.038$). This study defines the MTD and recommended phase 2 dose of PB at 27 g/day for heavily pretreated patients with recurrent gliomas. The pharmacology of PB appears to be affected by concomitant administration of P450-inducing anticonvulsants. *Neuro-Oncology 7, 177–182, 2005 (Posted to Neuro-Oncology [serial online], Doc. 04-018, February 16, 2004. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152851704000183)*

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[4] Abbreviations used are as follows: AA, anaplastic astrocytoma; AUC, area under the curve; CBC, complete blood count; C_{max}, maximum plasma concentrations; CR, complete response; DLT, dose-limiting toxicity; GBM, glioblastoma multiforme; KPS, Karnofsky performance status; MMSE, mini-mental status exam; MTD, maximum tolerated dose; NABTT, New Approaches to Brain Tumor Therapy; NCI, National Cancer Institute; PA, phenylacetate; PB, phenylbutyrate; PR, partial response; PT, prothrombin time; PTT, partial prothrombin time; SD, stable disease; T, plasma concentration time; T_{max}, time to C_{max}.

Differentiating agents may alter tumor growth and progression, slow or inhibit metastases, and/or affect response to other forms of therapy. Phenylbutyrate (PB)[4] is an aromatic fatty acid that is converted in vivo to phenylacetate (PA) by β-oxidation in liver and kidney mitochondria. The actions of PB as a differentiating agent are primarily related to its activity as an inhibi-

tor of histone deacetylase (Carducci et al., 1996). In vitro PB concentrations required to inhibit histone deacetylase and induce apoptosis begin at 0.5 mM of PB. In solid tumor cell lines, PB induces G_1/G_0 arrest and induces $p21^{waf1/cip1}$, a cell cycle checkpoint protein associated with differentiation and an inhibitor of histone deacetylase, within 24 h of treatment. Glioblastoma and prostate cancer cell lines exposed to PA and PB (Gore et al., 2002) at concentrations of 1 to 5 mM in vitro develop time- and dose-dependent growth arrest (Dmitrovsky et al., 1990; Samid et al., 1993). Human glioblastoma cells can undergo cell maturation and revert to a nonmalignant phenotype when exposed to these agents (Dmitrovsky et al., 1990; Hudgins et al., 1994; Sidell et al., 1995). In vivo studies exist for experimental gliomas in rats. Samid and colleagues administered PA to rats bearing intracranial glioma cells and showed suppression of tumor growth, more than 50% of the animals being rendered free of tumor when exposed to continuously administered PA (Samid et al., 1994). Phenylbutyrate had not been tested in these glioma models, but as a precursor in PA, and as a more potent agent, clinical studies of PB were warranted.

A phase 1 clinical trial of continuous intravenous infusions of PB in patients with refractory solid tumors demonstrated that this agent is safe and that doses of 410 mg/kg per day for five days every 21 days are well tolerated (Carducci et al., 2001). No complete responses (CRs) were noted; however, one patient with prostate cancer did have a partial response (PR). The dose-limiting toxicity (DLT) in this study was predominantly neurocortical. A phase 1 study of oral PB in 28 patients with solid tumors also showed that this agent was well tolerated. Oral bioavailability was 78%, and the maximum tolerated dose (MTD) was 27 g/day, with nausea/vomiting, neurocortical toxicity, and hypocalcemia being dose limiting at doses ⩾45 g/day (Gilbert et al., 2001). Both of these studies excluded patients with primary CNS tumors.

This study was designed to evaluate the safety, toxicity, and pharmacology of orally administered PB given three times daily to patients with recurrent high-grade gliomas until progression. In this clinical trial, we also studied the tolerability of continued exposure to oral PB, the ability to achieve plasma levels of >0.5 mM, and the impact of P450-inducing anticonvulsant drugs on the pharmacology of PB and its metabolites, and we examined preliminary evidence of therapeutic activity.

Patients and Methods

This study was conducted by the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium, which is funded by the National Cancer Institute (NCI) (Grossman et al., 1998a). This clinical research protocol was reviewed and approved by the Cancer Therapy Evaluation Program at NCI and the institutional review boards of all participating institutions. Informed consent was obtained from each patient who joined this research study. All patients eligible for this study were registered through the NABTT CNS Consortium's Central Operations Office in Baltimore, Md.

Patient Eligibility

Patients were eligible for this trial if they were over the age of 18 years, able to give informed consent, and understood the investigational nature of this study and its potential risks and benefits. In addition, they had to meet the following criteria: pathological confirmation of glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA), progressive measurable disease on CT or MRI scans following treatment with radiation therapy, sufficient time for toxicities of prior therapies to have resolved (3 months since radiation, >6 weeks since last nitrosourea or >4 weeks since other chemotherapy), Karnofsky performance status (KPS) of ⩾60%, life expectancy of at least three months, and adequate bone marrow function (white blood cells >2000/mm^3 or absolute neutrophil count >1500/mm^3, platelets >75,000/mm^3, and hemoglobin >9 g/dl), renal function (serum creatinine <1.7 mg/dl), hepatic function (total bilirubin <1.5 mg/dl and aspartate aminotransferase/alanine aminotransferase <4 times the upper limit of normal), and gastrointestinal function, as well as the ability to tolerate the large number of required PB pills. The patients were also required to have adequate cardiac and pulmonary function because of the propensity for PB to cause sodium retention, edema, and pleural effusions in animals.

Ineligible patients included those with uncontrolled hypertension, congestive heart failure, uncontrolled generalized tonic-clonic seizures (>1 per week), active infectious processes (including human immunodeficiency virus [HIV]), medical or psychiatric problems unrelated to the malignancy that might jeopardize compliance or put them at undue risk; connective tissue autoimmune diseases, dementia, or a mini-mental status exam (MMSE) score of <23. Patients were also excluded if they had received prior sodium PB or antineoplastons or if they were pregnant or breastfeeding.

Patient Evaluations

Prior to receiving the first dose of PB, patients underwent a complete history and physical exam; KPS evaluation; MMSE; tumor measurements; complete blood count (CBC) with leukocyte differential; determination of serum sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, calcium, magnesium, phosphorus, total bilirubin, liver transaminases, alkaline phosphatase, total protein, albumin, uric acid, prothrombin time (PT), and partial prothrombin time (PTT); urinalysis; pulmonary function test, electrocardiogram, chest X ray; and pathological confirmation of cancer diagnosis. Study evaluations during the first course of therapy included weekly CBCs with leukocyte differential and determination of serum sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, magnesium, phosphorus, calcium, PT, and PTT. These were obtained weekly for the first four weeks. For subsequent courses

CBC, electrolyte determination, chemistry panel, PT, and PTT were done every other week or monthly.

Treatment Plan and Drug Administration

Phenylbutyrate dose escalations were prespecified in the protocol to be 9, 18, 27, 36, and 45 g/day. The cycle length was 28 days, and intrapatient dose escalation was not allowed. PB was given orally in three equally divided daily doses continuously until there was evidence of disease progression, a 30-point decline in the KPS was observed, or patients requested to be withdrawn from study. Phenylbutyric acid, sodium salt ($C_{10}HNaO_2$) was administered as a 500-mg tablet that was to be administered with meals. This drug was provided under IND #50386 and NSD #657802 with supply from Targon Corporation (Princeton, N.J.) to NCI.

Compliance was assessed by using vial counts as well as patient calendars. Toxicity was assessed by using the NCI Common Toxicity Criteria (version 1.0). Pharmacologic studies were conducted during the first cycle of treatment for each patient as described below.

Dose-Limiting Event

Toxicities were scored according to the NCI Common Toxicity Criteria, version 1.0. Nonhematological toxicity of grade 3 or 4 was considered dose limiting. Hematological toxicity criteria for DLT were absolute neutrophil count $<500/mm^3$, either with fever or persisting more than three days, or thrombocytopenia $<50{,}000/mm^3$.

For purposes of this study, the MTD was determined by toxicity and patient compliance. The MTD was defined as the highest dose at which no more than one of seven patients experienced a drug-related DLT. Four patients were initially treated at a specified dose level. If no DLTs were noted at that dose, accrual began on the next highest dose level. If one of four patients experienced a DLT, three additional patients were accrued at the same dose. If two or more patients in a dose level experienced a DLT, then the MTD was considered to be exceeded, and three more patients would be treated at the next lower dose. Because of the large number of pills required in this study, patient compliance was also considered dose limiting. Adequate compliance was defined as ingesting 80% of the intended dose and not missing more than six doses a week. If two or more patients on a dose level did not meet the above criteria, then two additional patients would be added to that dose level to assess compliance. If three of the six patients were unable to meet the compliance standards, this was considered a dose-limiting event.

Response Assessment

Volumetric MRI or CT scans were obtained every eight weeks and evaluated according to the NABTT CNS Consortium's standard response criteria (Batchelor et al., 2004).

Pharmacokinetic Sampling and Analytical Assay

Pharmacokinetic studies were conducted during the first cycle of PB administration for each patient. Venous blood samples were collected on day 1 prior to administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h after PB administration. Samples were centrifuged at $1000 \times g$ for 10 min, and plasma was isolated and frozen at –20°C until the time of assay. Plasma PB and PA concentrations were quantified in plasma by reverse-phase high-performance liquid chromatography assay with UV detection as previously described (Gilbert et al., 2001). Calibrators for PB and PA covered the concentration range of 10 to 3000 μM. Quality assurance samples at low, medium, and high concentrations were assayed in triplicate with each analytical run; inter- and intra-day coefficients of variation were <10%.

Pharmacokinetic Analysis

Individual plasma concentrations for PB and PA in plasma were analyzed by using model-independent methods (Gibaldi and Perrier, 1982). Maximum plasma concentrations (C_{max}) and time to C_{max} (T_{max}) were the observed values from inspection of the concentration-versus-time curves. The terminal rate constant, k, was calculated as the negative slope of the log-linear regression of the terminal phase of the drug concentration-versus-time curve. The area under the curve (AUC) from time 0 to the time of the last quantifiable sample, AUC_{last}, was calculated by using the linear trapezoidal method as implemented in WinNonlin version 2.0 (Pharsight, Mountain View, Calif.). The AUC was extrapolated to infinity (AUC_{inf}) by dividing the last measured concentration by k. PB clearance was calculated as dose divided by AUC_{inf}. Systemic exposure of PA relative to that of PB was calculated as the AUC_{last} ratio of PA:PB. Pharmacokinetic data were described by using descriptive statistics. The Wilcoxon rank sum test was used to compare PB and PA pharmacokinetic parameters in the present study and those from patients with non-CNS solid tumor malignancies (Gilbert et al., 2001). The a priori level of significance was set at 0.05. Statistical analysis was performed by using JMP version 3.2.6 (SAS Institute, Cary, N.C.).

Statistical Considerations

Because PB was expected to produce minimal toxicity compared to cytotoxic agents, but has been associated with clinically significant limitations in patient compliance at high doses, the primary statistical objective of this study was to determine the MTD with respect to toxicity and compliance. A secondary objective was to look for preliminary evidence of therapeutic activity by using the outcomes of response and survival. Response was defined as a CR or PR. The response rate and exact binomial 95% confidence interval were calculated. Survival time was calculated from time of study entry until death or last follow-up. Overall survival was estimated by using the product-limit method (Kaplan and Meier,

1958) and performed with SAS software version 8.2 (SAS Institute, Cary, N.C.). All analyses were intention-to-treat analyses.

Results

Patients

Twenty-three patients were enrolled in this phase 1 study from November 1997 to September 1999. Three patients, whose data were used for dose escalation, were later found to be ineligible. One had a histological diagnosis of mixed glioma, one had a baseline MMSE <23, and one was found to have no measurable disease at baseline on central review of the MRI scan. These patients were eligible for toxicity and pharmacology evaluations, but were excluded from the efficacy analyses. Another patient met eligibility and began PB, but toxicity data were not received by the NABTT CNS Consortium Central Office. Therefore, that patient was replaced for dose escalation but was included in the survival analysis. Patient characteristics are listed in Table 1. Only three patients had brain biopsy without tumor removal. The median KPS was 80%, 16 patients scored ⩾80%, and seven patients scored <80%.

Dose Escalations, Toxicities, and Determination of the MTD

Dose escalations were prespecified in the protocol to be 9, 18, 27, 36, and 45 g/day. The principal toxicities are presented in Table 2. The starting dose of 9 g of PB daily was administered by using six 500-mg tablets three times each day. No DLTs were seen at this dose. At the second dose level of 18 g/day, one patient developed grade 3 headache and light-headedness. As a result, the cohort was expanded to seven patients. No DLTs were noted in the expanded cohort. At the 27-g/day dose level, four patients were treated without any DLTs. Four patients were subsequently treated at 36 g/day. Grade 3 CNS toxicity consisting of fatigue and somnolence occurred in two patients (50%) during the first cycle of their PB. Grade 3 anemia and neutropenia were also encountered in one (25%) of these patients. Because two out of four patients experienced a DLT at this dose level, three more patients were accrued to the previous dose level (27 g/day). One of these three patients had a DLT of grade 3 fatigue. Therefore, one out of seven patients had a DLT at a dose of 27 g/day, which was determined to be the MTD.

Table 1. Baseline demographic and clinical characteristics

Characteristic	N (%) or Median (range)
Total patients	23[a]
Sex—male	15 (65)
Race—white	19 (83)
Age, in years	51.4 (29.7–71.1)
Karnofsky performance status	80 (60–100)
Histology	
Anaplastic astrocytoma	5 (22)
Glioblastoma multiforme	17 (74)
Mixed glioma	1 (4)
Prior chemotherapy	
None	6 (26)
1 prior regimen	10 (43)
2 prior regimens	4 (17)
⩾3 prior regimens	3 (13)

[a] Total number of patients enrolled. Fewer patients were included in selected analyses as follows: Toxicity data were not obtained for one patient (n = 22), and three patients were later found to be ineligible and were not included in efficacy analyses (n = 20).

Therapeutic Activity

Of the 23 patients enrolled, 19 could be evaluated for tumor response. One CR and no PRs were noted, providing an overall response rate of 5% (95% confidence interval, 0–26%). Five patients (four GBM, one AA) demonstrated stable disease (SD) as the best response and a median time to progression of 5.4 months (range, 1.9–5.7 months). Thirteen patients (11 GBM, 2 AA) demonstrated progressive disease without a period of SD, and they all received fewer than four cycles of PB therapy. Fifteen patients were on enzyme-inducing antiepileptic drugs. Of note, four of the six patients with CR or SD were on enzyme-inducing antiepileptic drugs. Nineteen of the 20 patients who could be evaluated for survival have died. The total number of person-years of follow-up was 18.2, and the surviving patient has been followed for more than five years. Median survival time was 5.4 months.

Pharmacokinetic Studies

Of 23 patients treated, pharmacokinetic studies were performed for 21 patients. The PB and PA plasma pharmacokinetic parameters are listed in Table 3. At the recommended dose of PB for patients with CNS malignancies, 27 mg/m^2, the PB mean values for C_{max} and AUC_{inf} (standard deviation in parentheses) were 1225 (415) μM/h and 2487 (972) μM/h, respectively; for the metabolite PA, values were 617 (246) μM/h and 2437 (1180) μM/h, respectively. At all dose levels, the mean PB clearance was 22 liters/h (median, 20 liters/h). This was significantly higher (P = 0.038) than the mean PB clearance of 16 liters/h (median, 13 liters/h), which was observed in patients with non-CNS malignancies (Fig. 1A) (Gilbert et al., 2001). In the present study, three

Table 2. Grade 3–4 toxicities observed in cycle #1 by dose level[a]

	Dose Level (g/day)			
Toxicity	9 (n = 4)	18 (n = 7)	27 (n = 7)	36 (n = 4)
Headache	0	1	0	0
Light-headedness	0	1	0	0
Fatigue	0	0	1	2

[a] Toxicity data were not available for one enrolled patient, who was replaced for dose escalation. Therefore, only 22 patients are included in this table.

Table 3. Pharmacokinetic parameters for PB and PA in patients receiving 27g/day (n = 6)

PK Parameter	Mean	SD	Range
PB			
C_{max} (μM)	1225	415	628–1782
T_{max} (μM)	1.5	0.49	1.0–2.2
AUC_{last} (μM/h)	2472	968	1002–3755
AUC_{inf} (μM/h)	2487	972	1011–3774
Clearance (liters/h)	23	13	13–48
PA			
C_{max} (μM)	617	246	417–1098
T_{max} (μM)	3.3	0.65	2.5–4.2
AUC_{last} (μM/h)	2342	1124	1382–4401
AUC_{inf} (μM/h)	2437	1180	1396–4514
PA:PB AUC_{last} ratio	1.0	0.35	0.48–1.4

patients who did not receive treatment with anticonvulsant drugs had the lowest PB clearance values of 5.7, 5.8, and 10.7 liters/h (1 each at the 9-, 18-, and 36-g/day dose levels). The PB clearance values were more variable in patients with CNS malignancies than in those with non-CNS malignancies (Fig. 1A). Consistent with increased PB clearance and higher conversion of PB to PA, PA:PB AUC ratio values were significantly higher (P = 0.001) in patients with CNS malignancies (mean, 0.83; median, 0.80) than in those with non-CNS malignancies (mean, 0.46; median, 0.39) (Fig. 1B).

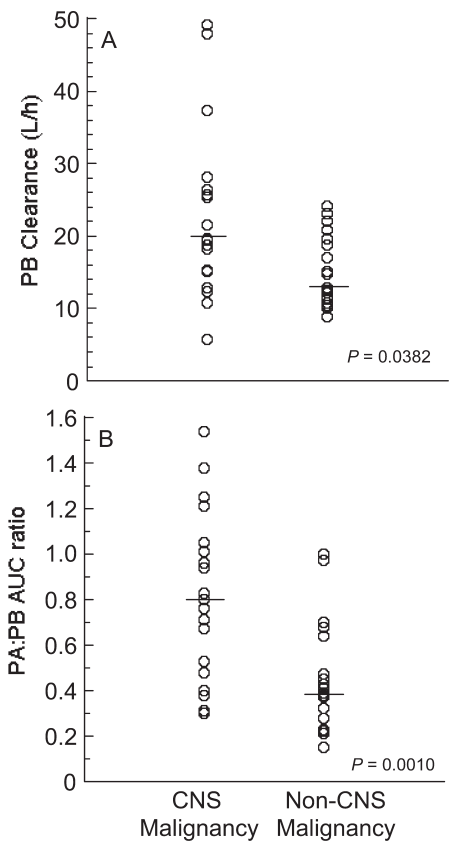

Fig. 1. Phenylbutyrate pharmacokinetics for patients with CNS malignancies (n = 21) and those with non-CNS malignancies (n = 19). A. PB clearance. B. PA:PB AUC ratio.

Discussion

This phase 1 clinical trial of oral PB demonstrates the safety of this agent in patients with recurrent high-grade gliomas at the recommended phase 2 dose of 27 g/day. The MTD identified in this study is somewhat lower than that seen in systemic malignancies where the DLTs were seen at 45 g/day (Gilbert et al., 2001) and the recommended phase 2 dose was 27 to 36 g/day. These data suggest that patients with CNS malignancies may be somewhat more likely to develop neurocognitive toxicities than patients without underlying neurologic abnormalities.

The coadministration of P450-inducing anticonvulsants has recently been shown to significantly affect the pharmacology of many chemotherapeutic agents (Fetell et al., 1997; Gilbert et al., 2003; Grossman et al., 1998b). This study suggests that the same is true for PB. The pharmacokinetics of PB and the metabolite PA following oral administration of PB at 9 to 45 g/day given in three equally divided daily doses have been reported for patients with non-CNS solid tumor malignancy (Gilbert et al., 2001). The average clearance value for PB was 16.0 liters/h. Exposure to PA represented 66% of that for PB, as determined by the PA:PB AUC ratio. At the recommended phase 2 dose of 27 g/day given daily and continuously in patients with non-CNS solid tumor malignancies, mean C_{max} values for PB and PA were 1680 and 589 μM, respectively; mean AUC values were 3779 and 2395 μM/h, respectively. Higher conversion of PB to PA was noted in the patients in this study than that observed in patients with non-CNS malignancies (mean values, 66% versus 83%), which may be due to concomitant treatment with anticonvulsants and a resultant increase in PB clearance (mean values, 16 liters/h vs. 22 liters/h). The potentially lower MTD in patients with CNS-malignancies (DLT at 36 g/day, MTD, 27 g/day) compared to patients with non-CNS malignancies (DLT at 45 g/day, MTD, 27–36 g/day) may be explained, in part, by higher conversion of PB to PA. Carducci, Gilbert and colleagues have shown that higher plasma PA exposure is associated with the severity of CNS toxicity (Carducci et al., 2001).

The potential importance of the higher dose of 36 g/day is underscored by the preclinical data (Carducci et al., 1996; Gore et al., 1997a, b; Warrell et al., 1998). At 36 g/day, the plasma concentration time (T) > 0.5 mM was 3.9 h, and thus a potentially active drug concentration was achieved for an extended period of time. At 27 g/day, the T > 0.5 mM was 3.2 h. It remains unclear as to what length of time is required for a therapeutic threshold for a biological effect, but this will have to be additionally explored in a phase 2 investigation.

As PB is a differentiating agent, SD and delayed tumor progression would be a desired outcome. However, in this study, one patient had a CR, five patients had SD ranging from 1.9 to 5.7 months, and the median survival was 5.4 months. The longest course of treat-

ment was 30 months, and one AA patient remained alive five years after study initiation (Baker et al., 2002). This represents a response plus SD rate of 32%, taking into account patients treated at all dose levels. The phase 2 study of PA by the North American Brain Tumor Consortium in 40 patients with recurrent malignant gliomas demonstrated 7.5% with PR, 17.5% with SD, and a median survival of eight months (Chang et al., 1999). No responses were observed in nine patients treated with an antineoplaston, which probably contains a similar active agent (Buckner et al., 1999).

This study suggests that oral PB is well tolerated in heavily pretreated patients with recurrent malignant gliomas at a dose of 27 g/day. A potentially important effect of concomitantly administered P450-inducing anticonvulsants has been described. Furthermore, about one quarter of treated patients had SD in response to single agent PB, and a single CR was observed. Although this study required patients to take a large amount of pills daily, more than 80% of all possible doses were taken by the patients. Oral PB remains a reasonable agent for further studies in patients with malignant gliomas.

References

Baker, M.J., Brem, S., Daniels, S., Sherman, B., and Phuphanich, S. (2002) Complete response of a recurrent, multicentric malignant glioma in a patient treated with phenylbutyrate. *J. Neurooncol.* **59**, 239–242.

Batchelor, T.T., Gilbert, M.R., Supko, J.G., Carson, K.A., Nabors, L.B., Grossman, S.A., Lesser, G.J., Mikkelsen, T., and Phuphanich, S. (2004) Phase 2 study of weekly irinotecan in adults with recurrent malignant glioma: Final report of NABTT 97-11. *Neuro-Oncol.* **6**, 21–27

Buckner, J.C., Malkin, M.G., Reed, E., Cascino, T.L., Reid, J.M., Ames, M.M., Tong, W.P., Lim, S., and Figg, W.D. (1999) Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin. Proc.* **74**, 137–145.

Carducci, M.A., Nelson, J.B., Chan-Tack, K.M., Ayyagari, S.R., Sweatt, W.H., Campbell, P.A., Nelson, W.G., and Simons, J.W. (1996) Phenylbutyrate induces apoptosis in human prostate cancer and is more potent than phenylacetate. *Clin. Cancer Res.* **2,** 379–387.

Carducci, M.A., Gilbert, J., Bowling, M.K., Noe, D., Eisenberger, M.A., Sinibaldi, V., Zabelina, Y., Chen, T.L., Grochow, L.B., and Donehower, R.C. (2001) A phase I clinical and pharmacological evaluation of sodium phenylbutyrate on a 120-h infusion schedule. *Clin. Cancer Res.* **7**, 3047–3055.

Chang, S.M., Kuhn, J.G., Robins, H.I., Schold, S.C., Spence, A.M., Berger, M.S., Mehta, M.P., Bozik, M.E., Pollack, I., Schiff, D., Gilbert, M., Rankin, C., and Prados, M.D. (1999) Phase II study of phenylacetate in patients with recurrent malignant glioma: A North American Brain Tumor Consortium report. *J. Clin. Oncol.* **17**, 984–990.

Dmitrovsky, E., Markman, M., and Marks, P.A. (1990) Clinical use of differentiating agents in cancer therapy. *Cancer Chemother. Biol. Response Modif.* **11**, 303–320.

Fetell, M.R., Grossman, S.A., Fisher, J.D., Erlanger, B., Rowinsky, E., Stockel, J., and Piantadosi, S. (1997) Preirradiation paclitaxel in glioblastoma multiforme: Efficacy, pharmacology, and drug interactions. New Approaches to Brain Tumor Therapy Central Nervous System Consortium. *J. Clin. Oncol.* **15**, 3121–3128.

Gibaldi, M., and Perrier, D. (1982) Noncompartmental analysis based on statistical moment theory. Chapter 11 in *Pharmacokinetics.* New York: Marcel Dekker. pp. 409–417.

Gilbert, J., Baker, S.D., Bowling, M.K., Grochow, L., Figg, W.D., Zabelina, Y., Donehower, R.C., and Carducci, M.A. (2001) A phase I dose escalation and bioavailability study of oral sodium phenylbutyrate in patients with refractory solid tumor malignancies. *Clin. Cancer Res.* **7,** 2292–2300.

Gilbert, M.R., Supko, J.G., Batchelor, T., Lessor, G., Fisher, J.D., Piantadosi, S., and Grossman, S.A. (2003) Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent glioma. *Clin. Cancer Res.* **9,** 2940–2949.

Gore, S.D., Samid, D., and Weng, L.J. (1997a) Impact of the putative differentiating agents sodium phenylbutyrate and sodium phenylacetate on proliferation, differentiation, and apoptosis of primary neoplastic myeloid cells. *Clin. Cancer Res.* **3,** 1755–1762.

Gore, S.D., Miller, C.B., Weng, L.J., Burks, K., Griffin, C.A., Chen, T.-L., Smith, V., Burke, P.J., Grever, M., and Rowinsky, E.K. (1997b) Clinical development of sodium phenylbutyrate as a putative differentiating agent in myeloid malignancies. *Anticancer Res.* **17,** 3938 (abstract 29).

Gore, S.D., Weng, L.J., Figg, W.D., Zhai, S. Donehower, R.C., Dover, G., Grever, M.R., Griffin, C., Grochow, L.B., Hawkins, A., Burks, K., Zabelena, Y., and Miller, C.B. (2002) Impact of prolonged infusions of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syndromes and acute myeloid leukemia. *Clin. Cancer Res.* **8**, 963–970.

Grossman, S.A., Fisher, J.D., Piantadosi, S., and Brem, H. (1998a) The New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium: Organization, objectives, and activities. *Cancer Control* **5**, 107–114.

Grossman, S.A., Hochberg, F., Fisher, J., Chen, T.L., Kim, L., Gregory, R., Grochow, L.B., and Piantadosi, S. (1998b) Increased 9-aminocamptothecin dose requirements in patients on anticonvulsants. *Cancer Chemother. Pharmacol.* **42,** 118–126.

Hudgins, W.R., Pineau, T., Sher, T., Gonzales, F.J., Myers, C.E., and Samid, D. (1994) Anticancer activity of phenylacetate and related aromatic fatty acids: Correlation with lipophilicity and capacity to activate nuclear receptor. *Proc. Am. Assoc. Can. Res.* **35**, 391 (abstract 2332).

Kaplan, E.L., and Meier, P. (1958) Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53,** 457–481.

Samid, D., Shack, S., and Myers, C.E. (1993) Selective growth arrest and phenotypic reversion of prostate cancer cells in vitro by nontoxic pharmacological concentrations of phenylacetate. *J. Clin. Invest.* **91**, 2288–2295.

Samid, D., Ram, Z., Hudgins, W.R., Shack, S., Liu, L., Walbridge, S., Oldfield, E.H., and Myers, C.E. (1994) Selective activity of phenylacetate against malignant gliomas: Resemblance to fetal brain damage in phenylketonuria. *Cancer Res.* **54**, 891–895.

Sidell, N., Wada, R., Han, G., Chang, B., Shack, S., Moore, T., and Samid, D. (1995) Phenylacetate synergizes with retinoic acid in inducing the differentiation of human neuroblastoma cells. *Int. J. Cancer* **60,** 507–514.

Warrell, R.P., Jr., He, L.Z., Richon, V., Calleja, E., and Pandolfi, P.P. (1998) Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. *J. Natl. Cancer Inst.* **90**, 1621–1625.